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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/121,587	07/23/98	CHAMBERS T	06132/033003

HM12/1227

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EXAMINER	
ZEMAN, M	
ART UNIT	**PAPER NUMBER**
1631	12

DATE MAILED: 12/27/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/121,587	Chambers, et al.
Examiner	**Group Art Unit**
Robert A. Zeman	1645

☒ Responsive to communication(s) filed on *Jul 23, 1998* .

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-16* is/are pending in the application.

Of the above, claim(s) *3-5 and 11-13* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1, 2, 4-6, and 14-16* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *3*

☒ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Priority

This application is a continuation-in-part application of PCT/US98/09894, filed on 3/2/98 which is a continuation-in-part application of 09/007,664 filed on 1/15/98, which is a continuation-in-part application of 08/807,445 filed 2/28/97, to which it claims priority to under 35 U.S.C. § 120.

Specification

The use of the trademarks YF-VAX®, JE-VAX® and ChimeriVax™ has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Election/Restriction

Applicant's election, without traverse, of the species of Japanese Encephalitis Virus, within group I in Paper No. 7 is acknowledged. Claims 3-5 and 11-13 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b) as being drawn to a non-elected species. Claims 17-29 are withdrawn from consideration as they are drawn to a non-elected invention.

Election was made **without** traverse in Paper No. 11. Applicant confirmed that examination would be limited to claims 1,2, 6-10 and 14-16, which read on the elected species, during a telephone interview on 12/17/99 (Interview summary attached).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 6-9 and 14-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an attenuated chimeric flavivirus comprising of a yellow fever virus whose prM-E coding sequence has been replaced with that of the Japanese Encephalitis virus, does not reasonably provide enablement for an attenuated chimeric flavivirus where the prM-E coding sequences are derived from other flaviviridae (Russian Spring-Summer Encephalitis virus or Omsk Hemorrhagic Fever virus for example). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. Applicant discloses the procedures for generating full-length cDNA templates for chimeric Yellow Fever viruses require unique restriction sites for *in vitro* ligation and the chimeric primers for engineering the C/prM and E/NSI junctions. (see page 45). However, applicant does not disclose the aforementioned details and it would require undue experimentation by one of skill in the art to make and use the invention as ~~disclosed~~ claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1,2, 6-10 and 14-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Venugopal et al. (Vaccine 12(11):966-975, 1994), Rice et al. (The New Biologist: 1(3):285-296, 1989), Marchevsky et al. (Am. J. Trop. Hyg. 52(1): 75-80, 1995), and Bray et al. (PNAS (USA) 88:10342-10346, 1991) and Chambers et al. (J. Virology 69(3): 1600-1605, March 1995).

The claims are drawn to a chimeric, live, infectious, attenuated virus, comprising: a yellow fever virus in which the nucleotide sequence encoding a prM-E protein is modified such that the functional YF virus prM-E protein is not expressed, and integrated into said YF virus a nucleotide sequence encoding a prM-E protein of a second, different flavivirus, specifically the Japanese Encephalitis virus, so that the prM-E protein of said second flavivirus is expressed. The claims are further drawn to the chimeric virus above wherein the nucleotide sequence encoding the prM-E protein of the second flavivirus comprises a mutation that prevents prM cleavage to produce M protein while maintaining the NS2B-3 protease recognition site and signal sequences and cleavage sites at the C/prM and E/NS1 junctions..

Venugopal et al. discloses the varied strategies which have been employed to generate flavivirus vaccines and immunogens. The section entitled "Genetically engineered live viruses derived from molecular clones" speaks to the production of chimeric viruses containing elements from different members of the flaviviruses. Venugopal et al. teaches the significance of the C-prM-E, prM-E or E genes of different flaviviruses to neurovirulence and suggests the replacement of these regions of one flavivirus with the corresponding genes of another flavivirus (page 972, 1st col. 2nd ¶). Venugopal et al. teaches that the complete or partial nucleotide sequence of the Japanese Encephalitis virus is well known and that full-length cDNA clones of the virus have been developed (page 967, 1st col., 1st ¶). Venugopal et al. even teaches introducing three distinct mutations into the Tick-borne Encephalitis virus (TBE) genome results in the ablation of the prM cleavage site and a reduction in neurovirulence (page 972, 1st col. 2nd ¶).

Venugopal et al. does not disclose a YF/Japanese Encephalitis (JE) chimera.

Rice et al. teaches that yellow fever (YF) virus is the prototypic member of the flavivirus family. More importantly, Rice et al. suggests employing yellow fever virus 17D cDNA templates as a carrier for neutralizing epitopes from heterologous flaviviruses such as dengue virus or Japanese encephalitis virus or other human pathogens (page 292, 2nd col. 3rd and 4th ¶s).

Marchevsky et al. suggests employing the well characterized 17D strain of yellow fever as a carrier for heterologous antigens.

Neither Marchevsky et al. nor Rice et al. teach a YF/Japanese Encephalitis (JE) chimera.

Bray et al. discloses the production of chimeras wherein the C-prM-E region of different dengue virus strains replace the C-prM-E region of dengue type 4. The choice of dengue type 4 appears to result from the availability of a full-length cDNA and the ability to make insertions into a common background. Bray et al. explicitly suggests insertion of another flavivirus, Japanese encephalitis virus for one, structural protein into dengue type 4.

Bray et al. does not disclose a YF/Japanese Encephalitis (JE) chimera.

Chambers et al. disclose that alterations of recognition sites, signal sequences and cleavage sites directly affect cleavage efficiency of NS2B-3. Many of the alterations that block or substantially reduce cleavage resulted in the loss of recoverable virus indicating that efficient cleavage at the 2B/3 site is required for flavivirus replication.

In view of the above teachings, it would have been obvious to one of ordinary skill in the art at the time of the claimed invention to have followed the methods of Bray et al. employing yellow fever virus cDNA template and Japanese encephalitis viruses to obtain a chimeric virus with the immunogenicity of Japanese encephalitis virus as suggested by Rice et al. and Marchevsky et al., while maintaining the integrity of the recognition sites and signal sequences, as suggested by Chambers et al., and having the well studied background of the yellow fever viral genome.

Conclusion

No claim is allowed

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert A. Zeman whose telephone number is (703) 308-7991. The examiner can be reached between the hours of 7:30 am and 4:00 pm Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, Donna Wortman, Primary Examiner can be reached at (703) 308-1032.

DONNA WORTMAN
PRIMARY EXAMINER

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December 21, 1999